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# Synthesis and Phosphorylation of 2-, 3-, and 4-Halomethyl-5-*tert*-butylfurans

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**Abstract**—Synthetic methods for preparing of 2-, 3-, and 4-halomethyl-5-*tert*-butylfurans are developed. It was established that the bromination of 3- and 4-methyl-2-*tert*-butylfurans with *N*-bromosuccinimide proceeds mainly at the free $\alpha$-position of the furan ring, and not at the methyl group. Therefore, the target halomethylfurans were prepared through the corresponding 3- and 4-methoxymethyl derivatives. The obtained five products were phosphorylated with sodium diethyl phosphite under the conditions of the Michaelis–Becker reaction to give the corresponding phosphonates.

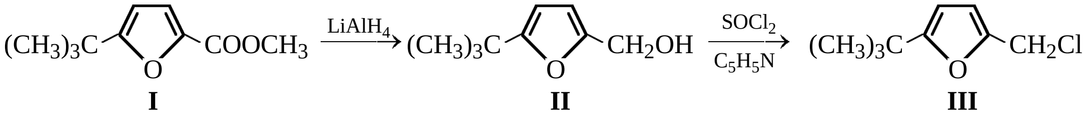
Synthesis and phosphorylation of polysubstituted halomethyl derivatives of 2-*tert*-butylfurans as well as the subsequent functionalization of the resulting products, mainly by nucleophilic substitution, were comprehensively studied by us previously.

At the same time, synthetic routes to dialkoxyphosphorylmethyl derivatives of 2-*tert*-butylfuran containing no electron-withdrawing substituent in the ring are poorly developed. These compounds are promising substrates for electrophilic substitutions in the furan ring, which do not occur in the presence of electron-withdrawing substituents.

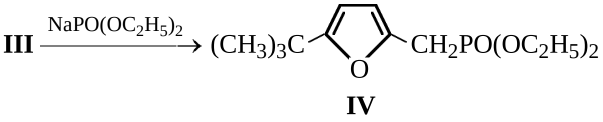
Halomethyl derivatives of 2-alkylfurans are often thermally unstable. Our previous works [1] showed that the compounds containing *tert*-butyl group are less prone to thermal dehydrohalogenation leading to rapid polymerization of the products. Therefore, the Michaelis–Becker reaction with these compounds must proceed more smoothly.

Thus, the goal of this work was to develop synthetic routes to halomethyl derivatives of 2-*tert*-butylfurans and study their phosphorylation under the conditions of the Michaelis–Becker reaction. The starting compounds for preparing the target products were accessible derivatives of 5-*tert*-butylfuran-2-carboxylic acid.

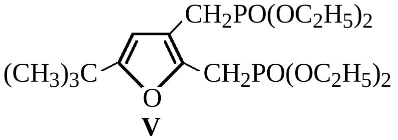
By reduction of ester **I** with lithium tetrahydroaluminate in ether, following the typical procedure [1], we obtained alcohol **II**. It is a fairly stable compound, which can be distilled in a vacuum and does not polymerize when stored at room temperature. Treatment of **II** with thionyl chloride in ether in the presence of pyridine at 5–10°C yields chloride **III**, which can be distilled in a vacuum (1 mm), but rapidly gets black when exposed to air. Therefore, it was involved in the Michaelis–Becker reaction immediately after the distillation.



Phosphorylation of chloride **III** with sodium diethyl phosphite was carried out in benzene at 80°C according to the typical procedure [1]. The reaction proceeded within 11 h. The target phosphonate **IV** was isolated by vacuum distillation in 38% yield.

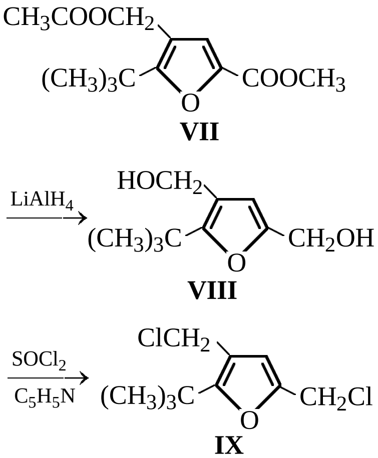


Recently, starting from alkyl 5-*tert*-butyl-2-bromomethylfuran-3-carboxylate, we prepared diphosphonate **V**.



**V**

Development of the procedure for chloromethylation of 5-*tert*-butylfuran-2-carboxylates [2] allowed us to attempt preparation of its 2,4-isomer **VI** starting from acetoxymethyl derivative **VII**.



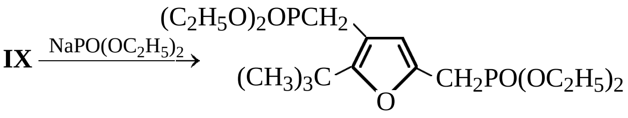
**VII**

**VIII**

**IX**

Reduction of **VII** with lithium tetrahydroaluminate in ether yields stable crystalline diol **VIII**. This diol was converted to bis(chloromethyl)furan **IX** by treatment with thionyl chloride in the presence of pyridine. This product can be distilled in a vacuum, but after isolation it fairly rapidly decomposes in air. Therefore, chloride **IX** was involved in the Michaelis–Becker reaction with 2 mol of sodium diethyl phosphite immediately after isolation. Contrary to chloride **III**, mixing of the reactants was accompanied by considerable heat evolution. Phosphorylation was carried out for 10 h at 80°C, and the target diphosphonate was isolated by vacuum distillation.

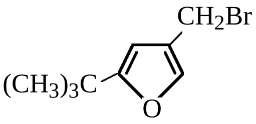
The product **VI** was isolated in 36% yield. It should be noted that the yields of compounds **IV** and **VI** isolated by the above procedure are determined, on the one hand, by chemical properties of the reactants and, on the other hand, by the stability of the target products under the conditions of isolation. In the course of isolation, diphosphonate **VI** endured two vacuum distillations at temperatures of up to 202°C; nevertheless, the yields of products **IV** and **VI** differ insignificantly. This fact suggests that the thermal stability of **VI** is very high.



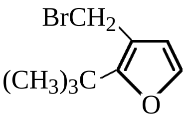
**VI**

We proposed to prepare β-dialkoxyphosphorylmethyl compounds **X** and **XI** through the key intermediates **XII** and **XIII** by the Michaelis–Becker reaction.

Several routes to halomethyl derivatives **XII** and **XIII** could be suggested, but the simplest route was bromination of methyl derivatives **XIV** and **XV** with *N*-bromosuccinimide (NBS).

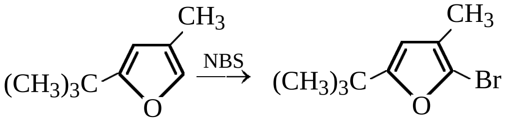


**XII**

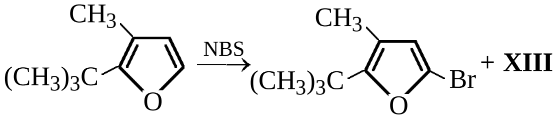


**XIII**

We found, however, that compound **XIV** is brominated in carbon tetrachloride in the presence of azobis(isobutyronitrile) exclusively at position 2 of the ring. Compound **XV** under the similar conditions gives a mixture of **XVI** and **XIII** in 3.4 : 1 ratio, according to the $^1$H NMR spectrum.



**XIV**



**XV**

**XVI**

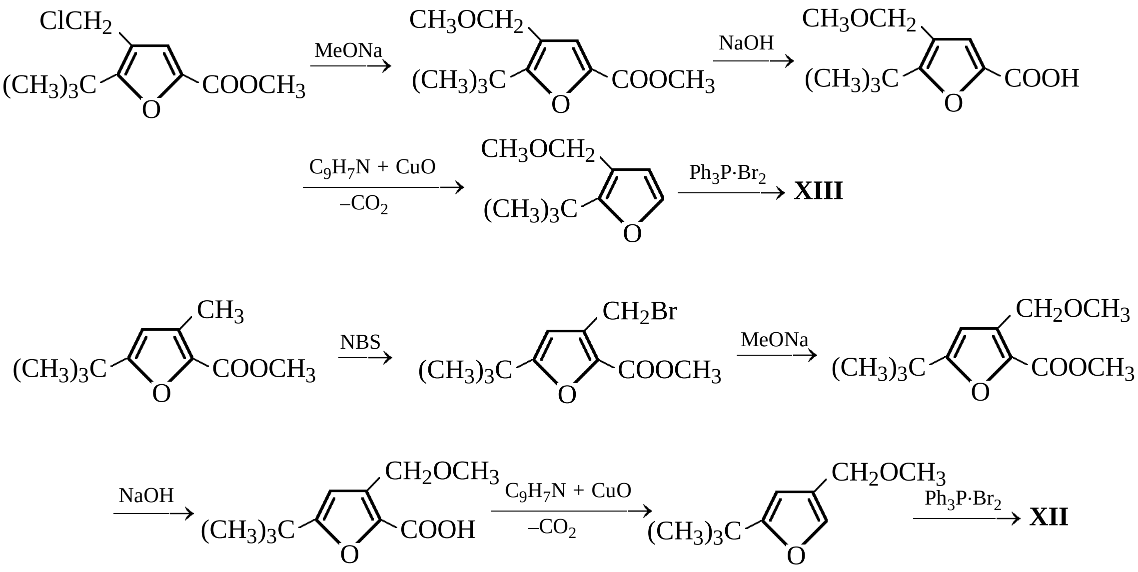
Therefore, we chose a route via methoxymethyl derivatives **XVII** and **XVIII**, which were prepared by Scheme 1.

The substitution of halogen with methoxy group was performed by the previously used procedure [3].

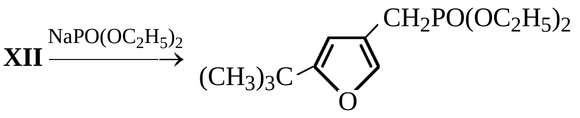
Furancarboxylic acids were decarboxylated with the quinoline–copper(II) oxide system at 200–220°C. Compounds **XVII** and **XVIII** were demethylated with triphenyldibromophosphorane in acetonitrile.

Bromides **XII** and **XIII** were phosphorylated with sodium diethyl phosphite in benzene by the standard procedure [1]. In both cases, the reaction occurred within 8 h. Under these conditions, the conversion of

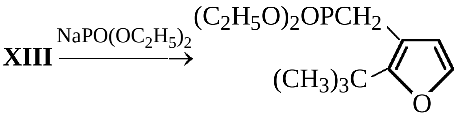
**Scheme 1.**



the bromides was complete, and phosphonates **X** and **XI** were obtained in 58% and 49% yields, respectively.

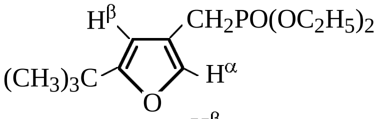


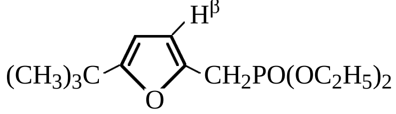
**X**



**XI**

We detected no products of the reduction of the bromomethyl group, characteristic of the reactions of furans containing electron-withdrawing substituents in the ring.





The $^1$H NMR spectra of phosphonates **IV**, **X**, and **XI** show an interesting feature. In **X** and **XI**, the coupling constant between the proton at the β-position of the ring and the phosphorus nucleus is virtually zero. In phosphonate **X**, the coupling constant between the phosphorus atom and $H^{\alpha}$ is 4 Hz, and in phosphonate **IV** with the reverse location of the substituents the remote coupling constant $J_{HP}$ is 2 Hz. Thus, the conductivity of the substituent effect in the furan ring is appreciably anisotropic.

## EXPERIMENTAL

The $^1$H NMR spectra were measured on Tesla BS-487C (80 MHz) and Tesla BS-497C (100 MHz) spectrometers. The phosphorus chemical shifts were calculated from the INDOR spectra.

**5-*tert*-Butyl-2-hydroxymethylfuran II.** To a suspension of 1 g of lithium tetrahydroaluminate in 30 ml of anhydrous ether, a solution of 6.2 g of methyl 5-*tert*-butylfuran-2-carboxylate **I** in 6 ml of anhydrous ether was added dropwise with stirring at a rate sufficient to maintain slight boiling of the reaction mixture. The resulting mixture was stirred for 2 h at room temperature and left overnight. After that, it was treated on cooling with 5 ml of ethyl acetate and decomposed with a saturated aqueous solution of ammonium chloride to phase separation. The ether solution was decanted and dried for 2 h over calcium chloride. The ether was evaporated, and the residue was distilled in a vacuum to give 3.6 g of alcohol **II**, bp 78–79°C (2 mm). $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.22 s [$(CH_3)_3C$], 4.10 s (OH), 4.30 s ($CH_2O$), 5.77 s ($H^4$-furan), 5.91 s ($H^3$-furan).

**2-(Diethoxyphosphorylmethyl)-5-*tert*-butylfuran IV.** *a.* A solution of 1.7 ml of thionyl chloride in 5 ml of ether was added dropwise with stirring at 5–10°C to a solution of 3.6 g of **II** and 2 ml of pyridine in 25 ml of ether. The resulting mixture was kept for 3 h at room temperature, the pyridine hydrochloride precipitate was filtered off, the ether was removed at reduced pressure, and the residue was distilled in a vacuum to give 2.3 g of chloride **III**, bp 46–48°C (1 mm), as a low-viscous oil quickly darkening in air. This product was immediately used for phosphorylation.

*b*. To a solution of sodium diethyl phosphite prepared from 0.3 g of sodium and 2.2 ml of diethyl hydrogen phosphite in 20 ml of benzene, 2.3 g of chloride **III** from the previous step was added at 70°C in one portion with stirring. The mixture was refluxed with stirring at 80°C for 11 h, sodium chloride was separated on a centrifuge, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 1.4 g (38%) of phosphonate **IV** as a light yellow oil, bp 129°C (1 mm). $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.19 m [$(CH_3)_3C$ + $CH_3$-ethyl], 2.99 d ($CH_2P$, $J_{HP}$ 21 Hz), 3.92 m ($CH_2OP$, $J_{HH}$ 7 Hz, $J_{HP}$ 10 Hz), 5.69 d ($H^4$-furan, $J_{HH}$ 2 Hz), 5.94 d.d ($H^3$, $J_{HH}$ 2 Hz, $J_{HP}$ 2 Hz).

**2,4-Bis(hydroxymethyl)-5-*tert*-butylfuran VIII.** To a suspension of 1.5 g of lithium tetrahydroaluminate in 50 ml of anhydrous ether, a solution of 7.1 g of methyl 4-acetoxymethyl-5-*tert*-butylfuran-2-carboxylate in 10 ml of anhydrous ether was added dropwise with stirring at a rate sufficient to maintain slight boiling of the reaction mixture. After the addition was complete, the resulting viscous mass was stirred for 3 h at room temperature and left overnight. Then the reaction mixture was decomposed with 10 ml of ethyl acetate and then with a saturated solution of ammonium chloride to phase separation. The ether layer was decanted, the ether was removed at reduced pressure, and the residue was kept for 1 h in a vacuum (1 mm) at room temperature. Diol **VIII** was obtained as a white crystalline mass, yield 5 g, mp 74–75°C. $^1$H NMR spectrum (DMSO-$d_6$, external $CF_3COOH$), δ, ppm: 1.86 s [$(CH_3)_3C$], 4.81 d ($CH_2O^4$, $J_{HH}$ 4 Hz), 4.96 d ($CH_2O^2$, $J_{HH}$ 4 Hz), 5.34 t, 5.64 t (OH), 6.70 s ($H^3$-furan).

**2,4-Bis(diethoxyphosphorylmethyl)-5-*tert*-butylfuran VI.** *a*. A solution of 3.7 ml of thionyl chloride in 5 ml of ether was added dropwise with stirring at 5–6°C to a solution of 4.7 g of diol **VIII** and 4.3 ml of pyridine in 40 ml of ether. The resulting mixture was kept at 10°C for 6 h, the pyridine hydrochloride precipitate was filtered off, the ether was removed at reduced pressure, and the residue was quickly distilled in a vacuum. Dichloride **IX**, 2.3 g, was obtained as a viscous liquid quickly darkening in air, bp 107°C (1 mm). The product was immediately involved in the Michaelis–Becker reaction.

*b*. To a solution of sodium diethyl phosphite prepared from 0.5 g of sodium and 3.2 ml of diethyl hydrogen phosphite in 25 ml of benzene, a solution of 2.3 g of dichloride **IX** in 5 ml of benzene was added in one portion with vigorous stirring at 70°C. The reaction mixture came to boil with strong foaming, and the precipitate of sodium chloride gradually formed. The mixture was refluxed with stirring for 10 h, sodium chloride was removed on a centrifuge, the solvent was distilled off at reduced pressure, and the residue was distilled in a vacuum. The fraction boiling in the range 168–202°C (1 mm) was collected and distilled once more to give 1.6 g (36%) of diphosphonate **VI**, bp 200–202°C (1 mm). $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.24 t ($CH_3$-ethyl, $J_{HH}$ 7 Hz), 1.35 s [$(CH_3)_3C$], 2.87 d ($CH_2P^4$, $J_{HP}$ 22 Hz, $\delta_P$ 24.2 ppm), 3.04 d ($CH_2P^2$, $J_{HP}$ 22 Hz, $\delta_P$ 19.7 ppm), 6.06 br.s ($H^3$-furan).

**2-Bromo-3-methyl-5-*tert*-butylfuran.** A mixture of 2.3 g of 3-methyl-5-*tert*-butylfuran, 3.1 g of *N*-bromosuccinimide, 0.1 g of azobis(isobutyronitrile), and 30 ml of $CCl_4$ was heated with stirring until an exothermic reaction started. After the heat evolution was complete, the mixture was heated with stirring for 1 h at 80°C. After that, no crystals of *N*-bromosuccinimide were observed on the bottom of the reaction flask. The mixture was cooled to room temperature, succinimide was filtered off, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 2.7 g of the product, bp 109°C (20 mm). $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.24 s [$(CH_3)_3C$], 1.87 s ($CH_3$-furan), 5.72 s ($H^4$-furan).

**Bromination of 2-*tert*-butyl-3-methylfuran with *N*-bromosuccinimide.** A mixture of 0.84 g of 2-*tert*-butyl-3-methylfuran, 1.44 g of *N*-bromosuccinimide, and 0.05 g of azobis(isobutyronitrile) was refluxed with stirring in 20 ml of $CCl_4$ for 1.5 h. After that, no crystals of *N*-bromosuccinimide were observed in the reaction mixture. The mixture was cooled to room temperature, succinimide was filtered off, and the filtrate was distilled in a vacuum to give 0.74 g of the fraction with bp 95°C (20 mm), quickly darkening in air without a solvent. $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 2-*tert*-butyl-3-methyl-5-bromofuran: 1.28 s [$(CH_3)_3C$], 2.01 s ($CH_3$-furan), 5.86 s ($H^4$-furan); 2-*tert*-butyl-3-bromomethylfuran: 1.36 s [$(CH_3)_3C$], 4.38 s ($CH_2Br$), 6.13 br.s ($H^3$-furan), 7.13 br.s ($H^2$-furan). The product ratio was 3.4 : 1.

**Methyl 4-methoxymethyl-5-*tert*-butylfuran-2-carboxylate.** A solution of 16.9 g of methyl 4-chloromethyl-5-*tert*-butylfuran-2-carboxylate in 50 ml of benzene was added in one portion to a solution of sodium methylate prepared from 1.7 g of sodium and 25 ml of methanol. The resulting mixture was stirred for 15 h at 60–62°C and poured into 100 ml of water.

The benzene layer was separated, the aqueous layer was extracted with dichloroethane, and the combined organic layers were washed with water to remove the residual methanol and dried over calcium chloride. After that, the solvent was removed at reduced pressure and the residue was distilled in a vacuum to give 13.2 g of the target product, bp 104–106°C (1 mm).

**2-*tert*-Butyl-3-methoxymethylfuran XVII.** *a*. Methyl 4-methoxymethyl-5-*tert*-butylfuran-2-carboxylate, 11.3 g, was heated with stirring with a solution of 6 g of potassium hydroxide in 30 ml of water for 4 h. The reaction mixture was cooled and acidified with hydrochloric acid to pH 1, and the oil that separated out was extracted with ether. The extract was washed with water and dried over calcium chloride, the ether was distilled off, and the residue was kept in a vacuum (1 mm) at room temperature for 1 h to give 9.2 g of 4-methoxymethyl-5-*tert*-butylfuran-2-carboxylate as a syrup.

*b*. The product from the previous stage, 9.2 g, was mixed with 6 g of freshly distilled quinoline and 0.3 g of copper(II) oxide. The mixture was heated with stirring and distillation of the volatile product. The fraction boiling in the range 162–210°C was collected and distilled in a vacuum to give 5.2 g of the target product with bp 84°C (20 mm), $n_D^{20}$ 1.4596. $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.26 s [$(CH_3)_3C$], 3.16 s ($CH_3O$), 4.19 s ($CH_2O$), 6.09 s ($H^4$-furan), 7.01 s ($H^5$-furan).

**2-*tert*-Butyl-3-bromomethylfuran XIII.** To a solution of 9.4 g of triphenylphosphine in 100 ml of dry acetonitrile, 1.9 ml of bromine was added dropwise with stirring at 0°C. The resulting suspension of triphenyldibromophosphorane was stirred for 20 min, and 6 g of 2-*tert*-butyl-3-methoxymethylfuran **XVII** was added in one portion. The reaction mixture was stirred for 8 h at 80°C, the major part of acetonitrile was distilled off at reduced pressure, and the residue was poured into 100 ml of a water–ice mixture. The resulting mixture was stirred for 15 min with 1 : 1 petroleum ether–diethyl ether mixture, triphenylphosphine oxide was filtered off, the organic layer was separated and dried over calcium chloride, the solvent was distilled off, and the residue was distilled in a vacuum to give 4.2 g of bromide **XIII**, bp 62–64°C (1 mm), $n_D^{20}$ 1.5070. $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.32 s [$(CH_3)_3C$], 4.32 s ($CH_2Br$), 6.13 br.s ($H^4$-furan), 7.12 br.s ($H^5$-furan).

**2-*tert*-Butyl-3-(diethoxyphosphorylmethyl)furan XI.** To a solution of sodium diethyl phosphite prepared from 0.45 g of sodium and 3.2 ml of diethyl hydrogen phosphite in 30 ml of benzene, 4.2 g of bromide **XIII** was added in one portion. The reaction mixture was stirred for 8 h at 80°C, the sodium bromide precipitate was removed on a centrifuge, the benzene was distilled off at reduced pressure, and the residue was distilled in a vacuum to give 2.6 g (49%) of phosphonate **XI**, bp 120°C (1 mm). $^1$H NMR spectrum, δ, ppm: 1.09–1.34 m [$(CH_3)_3C$ + $CH_3$-ethyl]; 2.86 d ($CH_2P$, $J_{HP}$ 21 Hz), 3.89 m ($CH_2OP$, $J_{HP}$ 11 Hz), 6.17 s ($H^4$-furan), 7.06 s ($H^5$-furan).

**2-*tert*-Butyl-4-(methoxymethyl)furan XVIII.** *a*. A mixture of 9.5 g of methyl 3-(methoxymethyl)-5-*tert*-butylfuran-2-carboxylate and a solution of 5 g of potassium hydroxide in 45 ml of water was refluxed with stirring for 3 h, cooled to room temperature, and acidified with hydrochloric acid to pH 1; the oil that separated out was extracted with ether. The extract was dried over calcium chloride, the ether was removed, and the residue was kept in a vacuum (1 mm) at room temperature for 1 h to give 7.1 g of 3-(methoxymethyl)-5-*tert*-butylfuran-2-carboxylic acid as a syrup.

*b*. A mixture of 7.1 g of 3-(methoxymethyl)-5-*tert*-butylfuran-2-carboxylic acid, 6 ml of freshly distilled quinoline, and 0.2 g of copper(II) oxide was heated with stirring and distillation of the volatile products. The collected fraction was distilled in a vacuum to give the product with the bp 102°C (20 mm), $n_D^{20}$ 1.4560. $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.17 s [$(CH_3)_3C$]; 3.17 s ($CH_3O$), 4.12 s ($CH_2O$-furan), 5.80 s ($H^3$-furan), 7.05 s ($H^5$-furan).

**2-*tert*-Butyl-4-bromomethylfuran XII.** To a solution of 6 g of triphenylphosphine in 100 ml of dry acetonitrile, 1.1 ml of bromine was added dropwise with stirring at 0°C. To the resulting suspension of triphenyldibromophosphorane, 3.6 g of furan **XVIII** was added in one portion, and the mixture was refluxed with stirring for 7 h. After that, the major part of acetonitrile was distilled off, and the residue was poured into 50 ml of ice–water mixture. A mixture of diethyl ether and petroleum ether (50 ml) was added to the reaction mixture, and the system was stirred for 30 min. Triphenylphosphine oxide was filtered off, and the organic layer was separated, dried over calcium chloride, and distilled in a vacuum to give 1.9 g of bromide **XII**, bp 57°C (1 mm), $n_D^{20}$ 1.4980. $^1$H NMR spectrum (DMSO-$d_6$, HMDS), δ, ppm: 1.26 s [$(CH_3)_3C$], 4.50 s ($CH_2Br$), 6.09 s ($H^3$-furan), 7.61 s ($H^5$-furan).

**3-(Diethoxyphosphorylmethyl)-5-*tert*-butylfuran X.** To a solution of sodium diethyl phosphite prepared from 0.4 g of sodium and 3 ml of diethyl hydrogen phosphite in 30 ml of benzene, 3.7 g of bromide **XII** was added with stirring at 80°C. The mixture was refluxed with stirring for 7 h, the sodium bromide precipitate was removed on a centrifuge, the benzene was removed at reduced pressure, and the residue was distilled in a vacuum to give 2.4 g (58%) of phosphonate **X**, bp 113°C (1 mm). $^1$H NMR spectrum ($CCl_4$, HMDS), δ, ppm: 1.13 t ($CH_3$-ethyl, $J_{HH}$ 7 Hz), 1.16 s [$(CH_3)_3C$], 2.64 d ($CH_2P$, $J_{HP}$ 22 Hz), 3.88 m ($CH_2OP$, $J_{HH}$ 7 Hz, $J_{HP}$ 11 Hz), 5.83 s ($H^4$-furan, $J_{HP}$ 4 Hz). $\delta_P$ 23.0 ppm.

## REFERENCES

1. Pevzner, L.M., *Zh. Obshch. Khim.*, 2002, vol. 72, no. 9, p. 1437.
2. Pevzner, L.M., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 11, p. 1812.
3. Pevzner, L.M., *Zh. Obshch. Khim.*, 2002, vol. 72, no. 1, p. 36.